Clinical Pharmacology Review: Pharmacokinetics

BLA: 97-0006

Product: Epogen/Procrit

Sponsor: Amgen

The pharmacokinetics of rHuEPO after iv and sc administration in adult normal volunteers and patients with chronic renal failure has been reported.

In both patients and normal volunteers, after iv administration of rHuEPO, serum levels decline in a monoexponential manner and the volume of distribution is similar to that of the plasma volume. The t1/2 in normal volunteers is approximately 5 hours. In patients with renal failure it is prolonged to approximately 9 hours. With multiple injections of rHuEPO, t1/2 and clearance decrease.

	Normal Volunteers, N=6		Chronic renal failure, N=5	
	single dose 150 U/kg	multiple dose 150 U/kg	single dose 150 U/kg	multiple dose 150 U/kg
Clearance, ml/h/kg	6.0±1	7.5±1.7	3.7±0.9	5.7±.8
T1/2, h	5.3	3.9	8.8	4.8
Vd, ml/kg	45.7±4.5	41.4±5.3	47.4±9.2	39.9±5.9

Table 1. Pharmacokinetics of rHuEPO in adult normal volunteers and patients with chronic renal failure[1] after iv administration.

After sc administration of rHuEPO, peak serum levels occur 12-24 h later. Peak serum levels are only 5% of the peak observed after a comparable iv dose. Serum t1/2 is approximately 20 h indicating that the rate of absorption into the systemic circulation is rate limiting. Area under the curve from 0 to 48 h after sc administration is 15% of the corresponding value after iv administration of an equivalent dose. Elevated levels of rHuEPO are found in the serum at 48 h, but not an iv dose.

---

1. Blood 76:1718, 1990.

The site of metabolism of rHuEPO are not know with certainty; however, both the liver and erythroid precursors participate in the process. Less than 5% of an injected dose is excreted unchanged in the urine.

King, et. al.[2] reported the pharmacokinetics of rHuEPO in two infants with renal failure less than 1 year old.

Due to persistent anemia and a low serum erythropoietin levels one infant was given rHuEPO (100 U/kg) sc 3 times weekly beginning at 31 days of age. The rHuEPO dose was increased on day 175 U/kg at day 46 and again on day 96 (250 U/kg).

Pharmacokinetic studies were performed on days 31 and 103 of age and analyzed using a biphasic model. Pharmacokinetic parameters are listed in Table 2. In comparison to data obtained in adults and previously cited in Table 1, it appears that both systemic clearance and the initial volume of distribution are increased.

Additionally, a decreased in the volume of distribution with repeated administration was observed in the child, a finding which was not observed in adults.

Total body water of full term neonates has been estimated to be 78% of body weight whereas this value for adults is about 60%. Fetuses and premature neonates have are 94% and 85% total body water. Total body water decreases during intrauterine life and continues to decrease to adulthood. Concurrent with the reduction in total body water is a shift in the distribution between intracellular and extracellular water. Whereas in neonate intracellular water comprises only 43% of total body water, with the remainder being extracellular body water (57%), in the adult intracellular body water comprises 68% of total body water with only 32% being extracelluar body water. These findings with regard to the distribution and per cent of body water in the infant relative to the adult,

With repeat dosing, a decrease in t1/2β, the half-life of the terminal elimination rate constant was observed. This change in t1/2β is analogous to the effect which occurs with repeated dosing in the adult. In the child reported in this study, the

[2]. J Pediatr 121: 822-5, 1992.

t1/2α was not observed to decrease with repeated dosing

	age 30 d, 100 U/kg iv	age 103 d, 250 U/kg iv
weight, kg	2.6	4.1
Cl, ml/hr/kg	12.6	14.8
Vd, ml/kg	82.8	57.8
Vss, ml/kg	120	79.8
t1/2α, h	1.3	1.6
t1/2β, h	7.4	4.8
MRT[3], h	9.5	5.1

Table 2. Pharmacokinetics of rHuEPO in a child age less than 1 year of age.

The authors also reported the pharmacokinetics of rHuEPO in a 29 day old boy weighing 2.8 kg with renal failure given rHuEPO iv (200 μg/kg). These results are reported below in Table 3. These findings resemble those reported above for an infant also less than 1 year of age.

	age 29 days, 200 U/kg
Cl, ml/hr/kg	12.4
Vd, ml/kg	75.8
t1/2α, h	0.9
t1/2β, h	7.8
MRT, h	10.3
Vss, ml/kg	127

Table 3. Pharmacokinetics in a boy - age 29 days.

3. Mean Residence Time

Montini, et. al.[4] studied the pharmacokinetics of rHuEPO in 24 children who ranged in age from 3 months to 18 years undergoing long-term peritoneal dialysis. rHuEPo was given sc at an initial dose of 25 IU/kg twice weekly. The response to rHuEPO in terms of hemoglobin concentrations was assessed at week 4. The dose was increased until a response was observed or precluded. Fourteen patients were assessed for their pharmacokinetics. No differences in age dependent pharmacokinetics were examined. No correlation was observed between increased hemoglobin concentrations and any pharmacokinetics endpoints determined in the course of the study. The results of the study are summarized in the table below.

	Number	Mean	Range
$AUC_{0-\infty}$, mU/ml/h	14	2242.9	574-7286
t1/2β, h	14	25.2	6.2-58.7
Clearance, ml/h/kg	14	17.7	3.4-43.5

Table 4. Pharmacokinetics of rHuEPO in children undergoing peritoneal dialysis.

Braun, et. al.[5] Investigated the single dose pharmacokinetics of rHuEPO given sc in 20 patients at different stages of chronic renal failure. These patients varied in weight from 17.0 to 59.8 kg and ages 7 to 20 years old. Patients were given 4,000 U/m2 sc. Two patients both 15 years of age were also given an iv dose (4000 U/m2) of rHuEPO. Pharmacokinetic endpoints were determined using non-compartment and 1-compartment models. Results are listed below in Table 4.

tmax, h	14.3±9.4
AUC∞, U/l/h	7,684±3.1
AUC-24h, U/l/h	3,731±1,603
Cl, l/h	0.6709±.37
t1/2, h	14.3±7.2

Table 5. Pharmacokinetics of pediatric patients with chronic renal failure given sc rHuEPO.

---

[4]. J Pediatr 122: 297 - 302, 1993.

[5]. Pediatr Nephrol 7: 61-64, 1993.

In the 2 children given both an iv and sc dose of rHuEPO, the absolute bioavailability was found to be 24% and 43%. When given by the sc route of administration peak serum levels (2,225 and 2554 U/L) are substantially reduced and delayed (tmax about 30 h) whereas clearance is reduced (0.277 and 0.279 l/h) in comparison to iv administration; furthermore, overall serum levels are significantly less. Like the situation in adults, it is likely that a `flip-flop' `condition' is operant after sc administration of rHuEPO. Under this condition, the rate of absorption is the rate limiting step in determining the pharmacokinetics of rHuEPO. Therefore, a true measure of the terminal t1/2 was not determined. (In this study, in fact, the terminal t1/2 was reported to be substantially shortened following sc administration in 1 individual - a finding which points out the experimental difficulties of using t1/2.) In comparison to adults, bioavailability in the pediatric population is approximately the same. Ateshkadi, et. al.[6] reported a bioavailability of 22.8% and a tmax of 17.1 h. Differences in tmax are relatively unimportant as sc administration yields relatively flat or constant infusional like state after the initial phase of absorption.

A study in pediatric patients with chronic renal failure on dialysis was reported by the sponsor. Originally the data were submitted in Oct 1987 (PLA 87-0536). In study EPO-8702, five patients (12 to 19 years of age) undergoing cycling peritoneal dialysis were given rHuEPO (150 U/kg) sc on 2 different occasions. Injections of rHuEPO were separated by 3 to 5 weeks between which patients had received at least 10 additional injections of rHuEPO. Various pharmacokinetics endpoints were assessed. Upon the first injection peak serum levels were found to be 475 to 600 mU/ml; whereas upon the second injection peak levels only achieved 110 to 250 mU/ml. AUC was also commensurately decreased between the two injections. The average AUC in the first injection period was 19.1 ± 2.0 and for the second injection period 4.3 ± 1.62. The relative bioavailability of the first and second injections was 12.9% to 32.3% in 3 patients. The mean t1/2 in patients appeared to be 14.5 h after the first and second injections. Due to practical and technical problems, a number of pharmacokinetic endpoints and subjects' data could not analyzed.

The pharmacokinetics of Epoetin alpha after iv administration were determined in 8 pediatric patients from 7 to 18 years old who were undergoing hemodialysis in study EPO-8905. Following a dose of 50 U/kg serum levels were measured over 24 h. In 3 patients the effect of repeated dosing on pharmacokinetics was observed. The pharmacokinetics of rHuEPO in pediatric patients

---

[6]. Am J Kidney Dis 21: 635-642, 1993.

was similar to that of adults. In this study, the volume of distribution was similar to that of the plasma volume (64.6±9.8 ml/kg)as was found in adults and the terminal elimination t1/2 were similar in this study as determined in an adult population (7.5±0.9 vs 9.3±3.2[7] h). Additionally, with repeated administration changes in t1/2 occurred which were similar in magnitude to adults. A 45% decrease in the t1/2 was observed in this study as versus a 33% decrease reported in an adult population in the original license application.

Martin D. Green

Martin D. Green, Ph.D.

[7]. Epoetin alfa license application, N=6